

with cardiac fibrosis ($p = 0.01$ and $p = 0.09$, respectively).

Conclusion: These results show the role of apoptosis in cell loss and the usefulness of fibrosis biomarkers (PICP, PIIINP) in cardiac remodeling during *T. cruzi* infection.

<http://dx.doi.org/10.1016/j.ijid.2012.05.382>

Type: Poster Presentation

Final Abstract Number: 50.005

Session: Animal Models, Pathogenesis & Host Defenses

Date: Friday, June 15, 2012

Time: 12:45–14:15

Room: Poster & Exhibition Area

Comparative efficacy of human simulated exposures of tedizolid and linezolid against *Staphylococcus aureus* in the murine thigh infection model

R.A. Keel¹, P.R. Tessier², J.L. Crandon^{2,*}, D.P. Nicolau²

¹ California Northstate, Rancho Cordova, CA, USA

² Hartford Hospital, Hartford, CT, USA

Background: We compared the efficacy of human simulated exposures of tedizolid (TR-700; formally torezolid) and linezolid (LZD) for the treatment of infection caused by *S. aureus* in the immunocompetent mouse thigh model.

Methods: 5 *S. aureus* isolates (3 MRSA; 1 VRSA; 1 MSSA) with TR-700 and LZD MICs ranging from 0.25–0.5 and 2–4 $\mu\text{g}/\text{mL}$, respectively, were utilized in the immunocompetent mouse thigh infection model. Two hours after inoculation, tedizolid phosphate and LZD were administered using a regimen that simulated the human steady state 24h area under the free concentration-time curve of IV TR-700 200mg Q24 and LZD 600mg Q12. Thighs were harvested and processed after 4, 8, 12, 24, 36, 48 and 72 h and efficacy was determined by the change in bacteria density at each of the timepoints relative to the 0 h controls.

Results: Human simulated exposures of both TR-700 and LZD resulted in similar efficacy against all tested *S. aureus* isolates. The mean bacterial density for control mice at 0 h was 6.89 log CFU/ml and the mean bacterial density increased to 7.34, 6.94, and 7.08 log CFU/ml after 24, 48, and 72 h, respectively. After 24h of treatment, >1 log CFU/ml reduction in bacterial density was observed for both agents (change in log CFU range: TR-700, 1.04–1.80; LZD, 1.36–2.02); whereas after 72h of treatment, antibacterial activity was enhanced for both agents with a reduction of >2.6 log CFU/ml (change in log CFU range: TR-700, 2.68–3.72; LZD, 2.64–3.76). Any statistical differences in efficacy between agents were transient and did not persist throughout the 72h treatment period.

Conclusion: Human simulated exposures of TR-700 200 mg Q24 and LZD 600 mg Q12 demonstrated similar in vivo efficacy against the *S. aureus* isolates tested. While both agents had bacteriostatic activity at 24h, this activity was enhanced with each day of dosing and ultimately resulted in bactericidal activity after the 3rd day of treatment. These data support the clinical utility of TR-700 for skin and skin structure infections caused by *S. aureus* as well as the bactericidal activity of the oxazolidinones after 3 days of treatment.

<http://dx.doi.org/10.1016/j.ijid.2012.05.383>

Final Abstract Number: 50.006

Session: Animal Models, Pathogenesis & Host Defenses

Date: Friday, June 15, 2012

Time: 12:45–14:15

Room: Poster & Exhibition Area

Advances in our understanding of the pathogenesis of rabies

A. Jackson

University of Manitoba, Winnipeg, MB, Canada

Background: It has been recognized that despite severe clinical illness, the neuropathology of rabies is relatively bland with mild inflammatory changes and few degenerative changes in neurons. This has led to the concept that the underlying abnormality is neuronal dysfunction, but the precise mechanisms remain uncertain.

Methods: We have evaluated neuronal structure in CVS- and mock-infected transgenic mice that express the yellow fluorescent protein. Because dorsal root ganglion (DRG) neurons are permissive for rabies virus infection *in vitro*, we used adult rodent DRG cultures to evaluate structural changes in the axons of CVS-infected cultures. We have assessed the cultures for a marker of lipid peroxidation with oxidative stress by immunostaining for 4-hydroxy-2-nonenal (4-HNE). Expression of NF- κ B was evaluated by Western immunoblotting and immunofluorescence in DRG neurons, and the effects of an activator (ciliary neurotrophic factor [CNTF]) and an inhibitor (SN50) of NF- κ B were evaluated. We also evaluated Krebs cycle enzyme activities and biochemical activities of the electron transport chain complexes.

Results: In CVS-infected mice there was extensive degeneration of neuronal processes explaining the severe clinical disease. *In vitro* infection of DRG neurons showed prominent axonal swellings associated with 4-HNE immunostaining and good viability of the neurons, indicating rabies virus-induced oxidative stress. CNTF was highly neuroprotective for CVS-infected neurons in reducing the number of 4-HNE-labeled puncta. SN50 and CVS infection had an additive effect in producing axonal swellings, suggesting that NF- κ B is neuroprotective. The fluorescent signal for p50 was quantitatively evaluated in the nucleus and cytoplasm of DRG neurons. At 24 hrs there was a significant increase in the nucleus:cytoplasm ratio, whereas at 48 and 72 hrs there was significantly reduced nuclear localization of NF- κ B in CVS infection. In CVS infection Krebs cycle enzyme activities were normal, whereas Complex I and IV activities were significantly increased vs. mock infection.

Conclusion: Neuronal dysfunction in rabies is associated with structural changes involving neuronal processes, which are mediated by oxidative stress. Rabies virus prevents nuclear activation of NF- κ B. Mitochondrial dysfunction likely plays a role in the increased production of reactive oxygen species (ROS). Increased activity of Complex I may lead to ROS overproduction due to reverse electron transfer.

<http://dx.doi.org/10.1016/j.ijid.2012.05.384>